

REMARKS

The Office Action dated June 27, 2003 has been reviewed carefully and the application amended in a sincere effort to place the same in condition for allowance. Reconsideration of the rejection and allowance of remaining claims 1-3, 5, 7-17 and 19-33 are respectfully requested on the basis of the following remarks.

The present invention has solved a number of problems in respect of existing procedures for isotope dilution mass spectrometry through the creation of speciated isotope dilution mass spectrometry which has capabilities above and beyond the existing state of the art in the former practices. The present invention provides for mathematical deconvolution of the species concentration, while correcting for species conversion and incomplete separation of the species from the sample. It also provides for species by species determination of concentration and for the creation of standards for use in such determinations.

These features among others are discussed throughout the specification including the extensive examples, which contain comparative data and confirmation of the operability of applicant's invention. See the examples beginning at the top of page 17 through page 45, line 10.

On page 42, line 12 through page 43, line 6, as well as shown in Figures 9(a) and 9(b), there is shown a dramatic contrast in the corrected concentration figures shown in the dotted legend in the bar diagram as contrasted with the uncorrected solid black figures.

Table II, which appears at the top of page 31 and the discussion regarding the same which begins at line 21 on page 31, provides an analysis of the successful performance of the SIDMS (speciated isotope dilution mass spectrometry) of the present invention along with a comparison contained in the last two columns of conventional isotope dilution mass spectrometry. Columns 9 and 10 of Table II, which columns bear the heading "Conventional IDMS" lists the results of using the IDMS approach contained in column 2 with resultant systemic errors as contrasted with the ability to correct for species conversion in addition to improving the precision and detection limits of the presently claimed invention.

Amended claim 1 is the sole independent claim. The claim with the present amendment recites providing a plurality of predetermined stable isotopes and also provides the clarifying amendment that if species conversion has occurred, it is corrected for by the claimed method.

The claim expressly recites the separation of "only a portion" of the species to be measured from the sample, thereby effecting incomplete separation, followed by isotope ratio determinations for each specie to be measured and mathematically deconvoluting the species concentration and if species conversion has occurred, correcting for the species conversion along with effecting mathematical deconvolution while correcting for the incomplete separation of the species from the sample.

Claim 1 clearly recites these distinguishing characteristics of the invention. More specifically, it is directed toward a method of speciated isotope dilution measurement of a sample which includes providing at least one predetermined stable isotope and preparing a different isotopic spike for each species to be measured by converting each stable isotope to a speciated enriched isotope corresponding to the species to be measured in the sample. The sample containing the species to be measured is spiked followed by equilibrating of the isotope-spiked species with the species to be measured.

The dependent claims further refine the recitals of claim 1.

Claims 1-3 and 5-33 - Section 112, second paragraph

With regard to the question raised in connection whether incomplete separation means (a) that less than all of the species in the sample are completely separated from the sample or (b) if the separation does not apply to complete separation between the specie being measured and at least one other specie in the sample, it could involve either category. The concept is as to a given species being measured only a portion of that species is separated from the sample which may contain other species and other materials. At page 46, lines 20-30 of the specification, it is stated that the invention can tolerate the loss of 90-95 percent of the species due to the species not being separated or being lost, converted or degraded. It further states that supplies to both species being separated from the sample, species containing sample, and from each other's species.

Claims 6 and 18 have been cancelled.

The cancellation of claim 6 obviates the objection as not further defining over claim 1. With regard to claim 32, the other claim rejected under Section 112, claim 32 has been amended to recite that "in addition to loss of said species due to said incomplete separation, a further reduction in said species occurred due to at least one cause selected from the group consisting of loss, conversion and degradation". It is respectfully submitted that this claim, as amended, does provide a refinement of claim 1 from which it depends directly.

In view of the cancellation of claim 6 and amendment of claim 32, it is respectfully submitted that the rejections under Section 112 have been obviated.

Claims 1-3, 5-33, Section 102(b) or Section 103(a)

Claims 6 and 18 have been cancelled.

The Section 102(b) rejection was on the basis of Kingston U.S. patent 5,414,259 and the Section 103(a) rejection was on the basis of Kingston in view of Suzuki-Sawada.

It is respectfully submitted that claim 1, as amended, is patentably distinct from the applied Kingston reference considered alone, in the context of Section 102(b) as well as when considered under Section 103(a) in the combination with Suzuki-Sawada. Among the significant distinctions set forth in amended claim 1 not taught or suggested by the Kingston reference are the following:

1. Kingston requires separation of all of the species from the sample, while the present invention can make an effective determination while "separating only a portion of said specie from said sample in order to effect incomplete separation". This is contrary to a basic teaching of the Kingston patent.

2. The present invention makes isotope ratio determinations for each specie to be measured and mathematically deconvolutes the specie concentration and if species conversion has occurred, corrects for species conversion.

Either one of these two basic distinctions alone are adequate to distinguish over the Kingston reference. In addition, claim 1 has further been amended to state that a plurality of predetermined stable isotopes are provided as contrasted with the prior recital which embraced the use of one.

In respect of the Examiner's reference to time resolution chromatography, it is important to note that the reference to use of the same to effect "separation of these species from the sample" is not entirely accurate, as in most instances, such chromatography cannot be used to separate species from the sample matrix. Such would be true, for example, in connection with soil samples such as was recited in Applicant's dependent claim 12, certain types of solid wastes, such as is set forth in dependent claim 14, as well as other complex matrices. Chromatography is more typically employed to separate a species from another species. The species and spikes in the present invention are extracted and incorporated in the extracts as in connection with soils and other solids, for example. In the practice of the present invention, the species and spikes are extracted and equilibrated in the extracts and then separated from the sample matrix before they can be subjected to chromatography which action would occur after separation from the sample. Where there is no solid matrix or competing species such as in a water sample, for example, the Kingston reference could employ chromatography for separation.

With regard to the reference toward the bottom of page 3 of the Office Action, column 8 of the Kingston patent, the reference equation on line 45 does not apply if the species has crossed over. Further, if there is crossover, the Suzuki-Sawada method will not correct for concentration differences. In addition, if there is not complete extraction from the sample, there would be no quantitative information emerging from using the Suzuki-Sawada teaching in combination with the Kingston reference.

In Suzuki-Sawada, the signal intensity which would be required for quantification in determination of concentration is not evaluated for the species of interest, the oligosaccharides, but rather for a derivative that has a different enhanced intensity, different mass and different chromatography as well as different chemistry. No way of relating the intensity of the derivative is disclosed in Suzuki-Sawada and no quantification is done. In the Suzuki-Sawada approach, intensity is directly proportional to concentration and bias and errors are inherent in this approach. As a result, the publication did not attempt to address quantifiable results as to these methods as contrasted with mere qualitative.

The numerous examples in Applicant's specification teach how to compensate for partial separation of the sample without relying on mass spectrometer resolution effects. Further to the Suzuki-Sawada teaching, it is important to note that there is no separation of actual species, but rather the creation of a new species that could be separated and involvement with complete separation of the new species. A comparison of Figure 3 with Figure 1 makes this apparent. In summary, the Suzuki-Sawada teaching is qualitative and not quantitative, lacks species separation from sample as contrasted with creation of a new species and is not readily combinable with Kingston without at least significant destruction of the individual teachings and, even if one were to force fit such a combination, would not render obvious the recitals of amended claim 1.

Further, with reference to paragraph 5 of the Office Action, the amended claim does recite the use of a plurality of predetermined stable isotopes.

Further to paragraph 5 of the Office Action, in respect to conversion between species, it is a feature of Applicant's invention that, as recited in amended claim 1, if species conversion has occurred, correction for the species conversion is effected. This recites an inherent capability of the process and deals with the problem of conversion. Much like one providing a mechanical filter which would filter out particles in excess of x millimeters in size, there is no need to claim the actual presence of such particles. It is part of the process in this hypothetical to remove such particles. Requiring the recital that they positively exist in every cycle of operation of a method would be improper. Reconsideration of this issue and recognition of the capability of Applicant's claimed process as set forth in amended claim 1 is respectfully requested.

The discussion on page 6 of the Office Action of the use of mathematical equations to correct resolutions of the analysis instruments, coupled with the teaching of Suzuki-Sawada, that when chromatography and mass spectrometer detection are combined, the difference in masses of the species within the sample can be used to separate the different specie even though chromatography alone could not effect this, is misdirected. For some of the reasons stated hereinbefore and, more importantly, Kingston teaches a very different method which recites withdrawal of all of a sample,

and from that point downstream is, therefore, not capable of performing the functions of Applicant's in making the quantitative determination in spite of incomplete separation of the species from the sample and species conversion. Further, for reasons stated hereinbefore, Suzuki-Sawada does not provide for separation of samples, but rather the creation of another sample and, in addition, is a qualitative and not quantitative teaching. Further, calibration of the mass spectrometer is not key to Applicant's successful achievement of the invention. Finally, as also stated, Applicant's claim 1 now recites a plurality of predetermined stable isotopes. This is also to be considered in the context of the limitations of time resolution chromatography in a respective complex matrix and solid samples.

It is respectfully submitted for the foregoing reasons that claim 1 is clearly patentable over the Kingston reference considered alone or Kingston combined with Suzuki-Sawada.

Dependent Claims 2, 3, 5, 7-17 and 19-33

Dependent claim 2 recites employing the method on more than one species simultaneously and dependent claim 3 recites quantification of Cr(III) and Cr(VI).

The features of claim 5 are claimed solely in the context of amended claim 1 from which it depends.

Dependent claim 8 recites employing the process on a sample which has experienced specie conversion prior to separation.

Claim 9 recites effecting equilibrium in an aqueous solution.

Claim 10 as amended recites employing the process on a plurality of said species to be measured and incompletely separating said species from other said species in said sample. This is inconsistent with the teaching of the cited Kingston reference. This formed no part of the original cited patent and is supported by data contained in Figures 9(a) and 9(b), and the related above-referenced examples. This portion of the method facilitates accomplishing a precise and accurate result on what otherwise might be considered an inadequate specimen.

Dependent claim 11, which depends from claim 3, recites effecting the separation after reduction of a substantial portion of Cr(VI) to Cr(III). Claim 12 recites employing the method on a soil sample and claim 13 recites employing it on an

aqueous sample. Claim 14 recites employing the process on solid waste from a chromite ore processing system. Solid samples present a different dimension of problem.

Claim 15 expressly recites storing the sample after the equilibrating step and prior to the separation step.

Dependent claim 16 recites effecting mathematical deconvoluting simultaneously with respect to more than one species to be measured. Claim 17, which depends from claim 16, recites effecting the mathematical deconvolution for each species independently of the other species.

Claim 19 recites separation of about 5-10 percent of each said species from the sample and from the other species before effecting said deconvolution. There is not such teaching or suggestion in the cited reference.

Claim 20, which depends from claim 1, recites preferred methods of separation employed in the context of the method of claim 1.

Claim 21 recites effecting the separation by microwave assisted extraction for a period of about 5 to 15 minutes. There is no such teaching in the cited reference. The data supporting this is discussed in the specification with respect to the Figure 10.

Claim 22, which depends from claim 21, recites effecting the separation at about 90° C to 150° C. These preferred approaches were not part of the cited reference.

Dependent claim 23 recites the method employed for purposes of validating another type of test. This is not taught or suggested by the cited reference.

Claim 24, which depends from 23, recites effecting a plurality of measurements by the other tests and effecting the comparison in evaluating the validity of the other tests.

Claim 25 recites a significant advancement in connection with the creation of speciated spiked standard materials. This subject was not dealt with at all in the cited Kingston patent.

Claim 26 depends from claim 1 and recites employing the method to prepare standard materials. Standards, as recited in claims 26 through 30 are very important, particularly in recognition of the fact that it is frequently difficult to effect complete

separation of a species from a sample. As a result, it is an important improvement of the present invention to permit the use of incomplete separation from the sample matrix. The reference for standard material can be prepared with isotopically enriched and prespiked species to enable a precise and accurate quantitative measurement even if complete removal of the species for the sample matrix and/or standard is not possible. The recitals of claims 26 through 30 provide quantitative means for comparing the results and calibration of the same. Claims 1 through 8 form a foundation for both the quantification of the unknown sample and the standard. They, thereby, enable species standardization even from complex sample matrices. In the portion of the specification beginning on page 44, line 17 under the heading Recovery of Insoluble and Non-Separated Component and carrying through page 45, line 10, there is given an example of difficult materials such as barium chromate and lead chromate which are not found in high concentrations in natural solutions partially due to solubility limitations. Accurate concentration determinations can be obtained by the present invention with only small portions of a percent of the specie being able to be separated.

Claim 27, which depends from claim 25, recites the creation of the new standards spiked with isotopically enriched species in different forms.

Claim 28, which depends from claim 26, recites employing the standard materials after storage. The cited reference did not deal with such concepts.

Claim 29, which depends from claim 26, recites employing the method to correct species shifts in the standard material after degradation.

Claim 30, which depends from claim 21, recites employing in the microwave extraction closed vessel microwave extraction.

Dependent claim 31, which depends from claim 23, recites the contribution of the method validating tests, which are “not independently capable of compensating for incomplete species extraction or species conversion.” The specification discussion regarding Figures 9(a) and 9(b) is related to this feature, as is the specification discussion at page 44, line 17 through page 45, line 10.

Dependent claim 32 recites performing the method on a species, which due to incomplete separation and an additional source of reduction of specimen selected

from the group consisting of loss, conversion, and degradation has less than 10 percent of this species separated. This ability to accomplish the objective of speciated isotope dilution measurement on an incomplete specimen is not taught or suggested by the reference.

Claim 32 also recites less than 10 percent of the species being separated. This does not involve new matter as the basis is found on page 46, lines 20 through 31.

Finally, dependent claim 33 depends from claim 32 and recites effecting the separation of at least about 5-10 percent of the species. This recites the fact that the invention will work successfully even with such a relatively small portion of the sample.

It is respectfully submitted that claims 1-3, 5, 7-17 and 19-33 are patentable over Kingston considered alone or in combination with Suzuki-Sawada.

MISCELLANEOUS

The additional art made of record, but not applied has been reviewed, but is not believed to be as relevant as the applied art.

SUMMARY AND CONCLUSIONS

In view of the foregoing, it is respectfully submitted that the cancellation of claim 6, amendment of claim 32 and explanatory remarks have obviated the Section 112, paragraph 2 rejections and that amended claim 1 as well as the remaining claims which depend directly or indirectly therefrom are patentable over the prior art. It is respectfully submitted that the application is now in proper form for issuance of a Notice of Allowance and such action is respectfully requested at an early date.

Respectfully submitted,



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